C–H Activation Hot Paper

International Edition: DOI: 10.1002/anie.201604268
German Edition: DOI: 10.1002/ange.201604268

Catalytic C(sp^3)–H Arylation of Free Primary Amines with an *exo* Directing Group Generated In Situ

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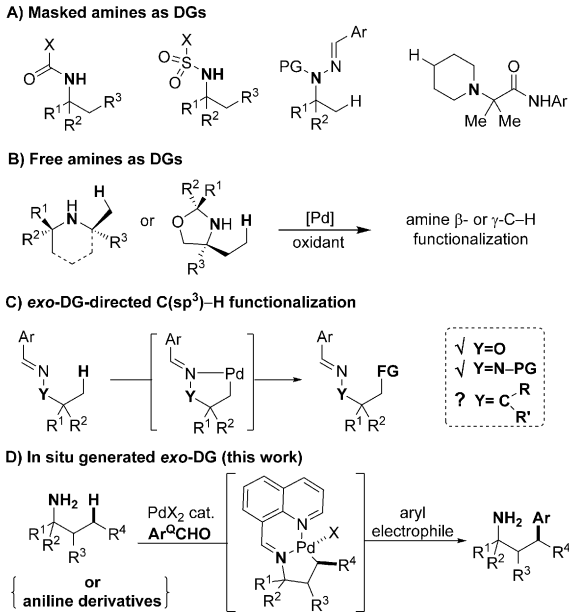
Dedicated to Professor Barry M. Trost on the occasion of his 75th birthday

Abstract: *Herein, we report the palladium-catalyzed direct arylation of unactivated aliphatic C–H bonds in free primary amines. This method takes advantage of an exo-imine-type directing group (DG) that can be generated and removed in situ. A range of unprotected aliphatic amines are suitable substrates, undergoing site-selective arylation at the γ-position. Methyl as well as cyclic and acyclic methylene groups can be activated. Furthermore, when aniline-derived substrates were used, preliminary success with δ-C–H arylation was achieved. The feasibility of using the DG component in a catalytic fashion was also demonstrated.*

Amines are commonly found in approved drugs, agrochemicals, and other biologically important molecules.[1,2] While still an on-going challenge, the site-selective functionalization of unactivated C–H bonds[3] in amines would offer a straightforward approach to access various derivatives and analogues, which should consequently impact the development of pharmaceuticals and agrochemicals. During the past decade, significant progress has been made in terms of the transition-metal-catalyzed functionalization of unactivated aliphatic C–H bonds in amines by using directing group (DG) strategies,[4] in which the amine moiety is often masked as an amide,[5,6] sulfonamide,[7] hydrazone,[8] or urea,[9] or tethered with another DG[10] (Scheme 1 A). Albeit highly effective, these tactics typically require additional steps for the installation and removal of the DG component. An ideal approach would directly employ a free amine as the DG. Recently, Gaunt and co-workers disclosed the first examples of free-amine-directed catalytic activation of primary C–H bonds (Scheme 1 B); in their study, the use of bulky, disubstituted amine substrates appeared to be important.[11] It is likely that the main difficulties of directly using a free amine as the DG result from the lack of backbonding when coordinated to transition metals as well as the susceptibility of amines to both oxidants and electrophiles.[12]

Inspired by the aforementioned challenge, we sought to use an in situ generated, *exo*-type DG (with the π-bond of the DG outside the metallacycle) for the direct C–H activation of free primary amines. Our laboratory has recently employed an *exo* directing mode to realize the catalytic functionalization of unactivated aliphatic C–H bonds with oximes[13] and hydrazones[8] (Scheme 1 C, Y = O and N-PG). An intriguing question is whether a regular imine (Y = CRR′) can be employed as an effective *exo*-DG for C(sp^3)–H activation. Compared to oximes and hydrazones, *N*-alkyl imines are generally more labile towards hydrolysis; however, the successful realization of such a transformation would enable the use of free amines as substrates for remote C–H functionalization through in situ formation and removal of the imine DG (Scheme 1 D).[14–16] Seminal examples of using aniline-derived imines as *exo*-DGs were reported by Sames and co-workers in the total synthesis of rhazinilam[17] and the core of teleocidin B4;[18] these syntheses involved the use of stoichiometric amounts of platinum and palladium for dehydrogenation, vinylation, and carbonylation reactions. Herein, we describe the development of a Pd-catalyzed direct arylation of the unactivated γ- and δ-C–H bonds in free primary alkyl amines and anilines by using an 8-formylquinoline-derived *exo*-DG, which enables the functionalization of methyl as well as acyclic and cyclic methylene groups.

Simple 2-butylamine (**1a**) was employed as the initial model substrate. To generate the imine DG in situ, quinoline-



Scheme 1. DG-based strategies for amine C(sp^3)–H functionalization. PG = protecting group.

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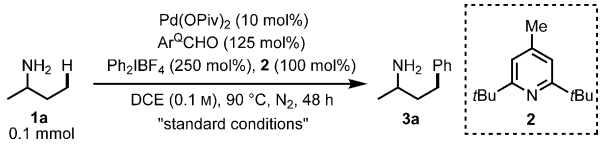
Supporting information for this article can be found under: http://dx.doi.org/10.1002/anie.201604268.

8-carbaldehyde (Ar^QCHO) was employed as the additive owing to our previous success with this type of *exo*-DG.[13b] After carefully examining a range of Pd precatalysts, additives, and solvents, the desired γ-arylation product (**3a**) was obtained in 75% yield when $Pd(OPiv)_2$ was used as the precatalyst, an aryl iodonium salt (Ph_2IBF_4) as the electrophile, base **2** as the additive, and dichloroethane (DCE) as the solvent (Table 1, entry 1). The C–H arylation occurred site-selectively at the γ-position, and no β-arylation was observed, which is likely due to the preferred formation of the five-membered palladacycle.

A series of control experiments were subsequently conducted (Table 1). In the absence of either the Pd precatalyst or quinoline-8-carbaldehyde, the desired product was not observed (entries 2 and 3). The yield significantly diminished when the reaction was run under air or at a lower temperature (entries 4 and 5). The use of $Pd(OAc)_2$ instead of $Pd(OPiv)_2$ gave comparable results (entry 6). The counterion of the iodonium salt slightly affected the efficiency of this transformation, with BF_4 being optimal (entries 7 and 8). A bulky, non-coordinating substituted pyridine base (**2**) was employed to neutralize the HBF_4 generated, but insoluble inorganic bases, such as $Ba(OH)_2$, were also effective (entry 9). Finally, whereas DCE proved to be the best solvent (entries 10 and 11), the reaction tolerated a stoichiometric amount of water (entry 12).

The substrate scope of the γ-arylation was then explored (Table 2). Although the arylated free amine products could be isolated upon workup (see below, Scheme 2), for ease of isolation and also owing to the volatility of the alkyl amines, all of the products were isolated as the benzoylamide derivatives. Aryl groups with various electronic properties were installed under the reaction conditions (**4a**–**4h**). Furthermore, primary, secondary, and tertiary alkyl amines are all suitable substrates for this reaction (**4i**–**4l**). A number of

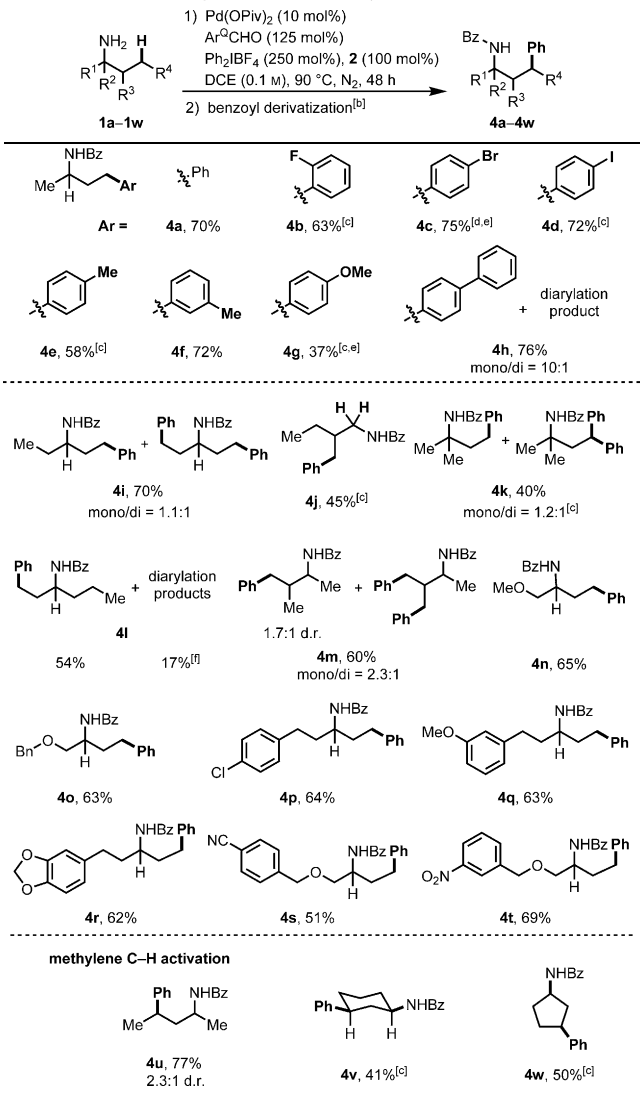
Table 1: Control experiments for the γ-arylation of amine **1a**.



Entry	Variations from the standard conditions	**3a** [%][a,b]	Unreacted **1a** [%][a,b]
1	–	**75**	**10**
2	no $Pd(OPiv)_2$	0	73
3	no Ar^QCHO	0	50
4	under air	36	18
5	at 70 °C	< 10	74
6	$Pd(OAc)_2$ instead of $Pd(OPiv)_2$	71	7
7	Ph_2IOTf instead of Ph_2IBF_4	61	24
8	Ph_2IPF_6 instead of Ph_2IBF_4	65	18
9	$Ba(OH)_2$ instead of **2**	56	23
10	in $CHCl_3$	41	29
11	in PhCl	24	54
12	with H_2O (1 equiv)	70	15

[a] Determined by ^1H NMR spectroscopy using 1,1,2,2-tetrachloroethane as the internal standard. [b] Sum of the protonated amine and the corresponding imine condensed with Ar^QCHO. Piv = pivaloyl, Tf = trifluoromethanesulfonyl.

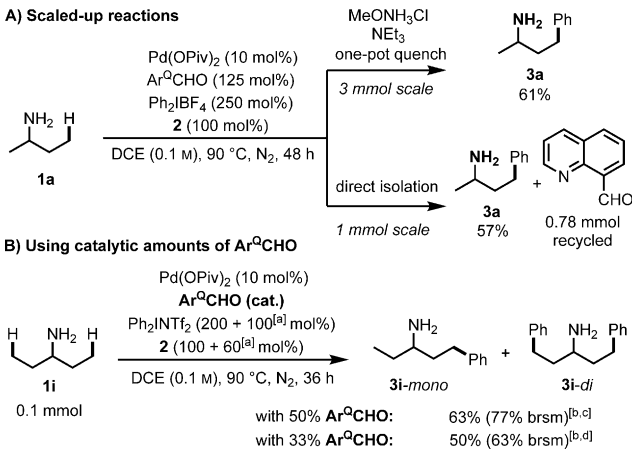
Table 2: Substrate scope with various alkyl amines.[a]



[a] All yields refer to the isolated products. Unless otherwise noted, the *gem*-diarylation products were observed in less than 5%. [b] Benzoylation procedure: $MeONH_3Cl$ (4.0 equiv), NEt_3 (0.3 mL), RT, 2 h; then Bz_2O (8.8 equiv), RT, 12 h. [c] 100 °C. [d] 105 °C. [e] 64 h. [f] The 1,1- and 1,5-diarylation products were isolated in a ratio of 1:4; the 1,5-diarylation product was formed in 3:1 d.r. For details, see the Supporting Information. Bz = benzoyl.

functional groups, including electron-rich arenes (**4g**, **4q**, and **4r**) and benzyl ethers (**4o**, **4s**, and **4t**) as well as methylenedioxy (**4r**), cyano (**4s**), and nitro (**4t**) groups, were compatible with the reaction conditions. It is noteworthy that aryl chlorides (**4p**), bromides (**4c**), and iodides (**4d**), although known to undergo Pd-catalyzed arylation reactions,[5–7] were tolerated by this catalytic system, so that they can be used as a handle for further functionalization. Remarkably, both cyclic and acyclic methylene C–H bonds can be arylated with good efficacies (**4u**–**4w**).

Isolation of the free amine products proved to be feasible. After a simple workup with methoxyamine, free amine product **3a**, though volatile, was still isolated in 61% yield on a 3 mmol scale (Scheme 2A). Furthermore, **3a** could be



Scheme 2. Further studies on C–H γ-arylation. [a] A second batch of the oxidant and base was added after 18 h. [b] Determined by ^{1}H NMR spectroscopy using 1,1,2,2-tetrachloroethane as the internal standard. The product was observed as a mixture of the protonated amine and the corresponding imine after condensation with Ar^{Q}CHO. [c] Mono/di = 1:1.4. [d] Mono/di = 1:1.5. brsm = based on recovered starting material.

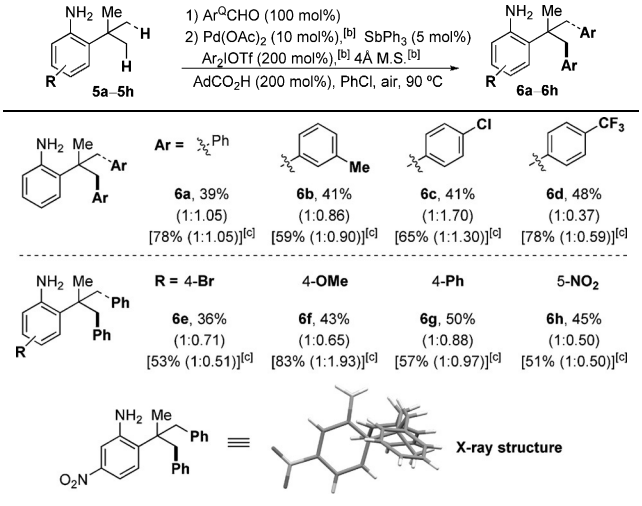
directly isolated from the reaction mixture (without methoxyamine workup) by chromatography, affording **3a** in only slightly decreased yield while recycling most of the Ar^{Q}CHO (Scheme 2A). Furthermore, owing to the reversibility of the imine formation, the use of a catalytic amount of Ar^{Q}CHO was examined. To our delight, moderate catalytic activity was observed, suggesting that imine formation and hydrolysis are compatible with the C–H arylation conditions (Scheme 2B). Higher yields were obtained when the oxidant and base were added in two batches.

Apart from alkyl amines, preliminary success was also achieved for the C–H arylation of aniline-derived substrates (Table 3). When 2-*tert*-butylaniline (**5a**) was employed as the model substrate, δ-arylation was achieved under modified reaction conditions (for detailed optimization studies, see the Supporting Information). Ar^{Q}CHO again afforded the optimal DG. Whereas generating the DG in situ provided the desired arylation product, higher yields were achieved when the imines were preformed simply by premixing Ar^{Q}CHO and the amine substrate for 1 h and removing the solvent in vacuo. Interestingly, $SbPh_3$ is an effective additive to achieve consistent yields, although its exact role remains unclear. Molecular sieves (4 Å) are critical for the arylation of aniline **5a**. Saturation of the molecular sieves with water (100 μL added) led to no significant drop in yield, though their replacement with base **2** inhibited the reaction.[19] 1-Adamantanecarboxylic acid ($AdCO_2H$) also played a pivotal role, likely promoting the C–H cyclopalladation step. Unlike the γ-arylation reaction, this transformation can tolerate air. Moreover, the aniline products could be directly isolated upon workup without the need for further derivatization.

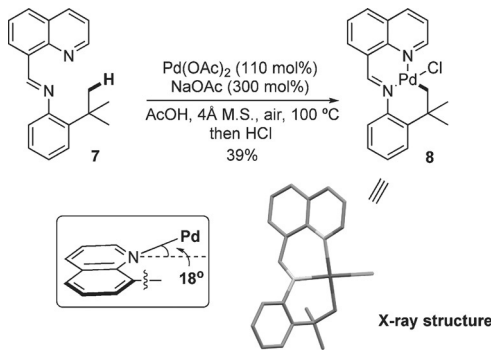
To better understand the role and coordination mode of the *exo*-DG, we sought to explore the reaction of imine **7** with stoichiometric Pd (Scheme 3).[20] Gratifyingly, palladacycle **8** was formed when using HOAc as the solvent and subsequently isolated, which enabled its characterization by X-ray crystallography. Interestingly, when CD_3COOD was used as the solvent, no deuteration of the *tert*-butyl group was observed, suggesting that the cyclometalation might not be an equilibrium process under these conditions.[6q] The crystal structure of **8** shows that while still maintaining a square-planar geometry, the Pd center is removed from the quinoline plane by 18°, which was not the case for a previously reported palladacycle formed by amide-directed C–H metalation.[6q]

In summary, we have developed a method for the palladium-catalyzed direct arylation of C(sp^3)–H bonds in free primary amines. Using an in situ generated imine *exo*-DG, a range of unactivated aliphatic C–H bonds, including methyl as well as cyclic and acyclic methylene groups, were site-selectively activated. Given the excellent functional-group compatibility and the ubiquity of amine functional groups, it is expected that this method will streamline the synthesis of nitrogen-containing compounds. The use of in situ generated *exo*-DGs through the formation of dynamic covalent bonds should also have broad implications beyond this work. Efforts towards expanding the scope of this process, particularly with aniline substrates, and enhancing the cata-

Table 3: Substrate scope with aniline-derived substrates.[a]



[a] Yields of isolated products are given. [b] Added in two portions. [c] Yields determined by ^{1}H NMR spectroscopy using 1,1,2,2-tetrachloroethane as the internal standard; the ratio of the mono- and diarylated products is given in parentheses. Ad = adamantyl.



Scheme 3. Stoichiometric formation and isolation of palladacycle **8**.

lytic reactivity with the DG component ($Ar^{Q}CHO$) are underway.

Acknowledgements

We thank the Frasche Foundation, the ACS PRF, and the Welch Foundation (F-1781) for funding. G.D. is a Searle Scholar and Sloan Fellow. D.M.M. thanks the NSF (CAREER; CHE-1254935) for the program "Research Experience for Veteran Students". We thank Dr. Vince M. Lynch and Dr. Amber M. Johnson for assistance with X-ray crystallography and purification, respectively. Johnson Matthey is thanked for a generous donation of Pd salts.

Keywords: arylation · C–H activation · directing groups · palladium catalysis · primary amines

How to cite: *Angew. Chem. Int. Ed.* **2016**, *55*, 9084–9087
Angew. Chem. **2016**, *128*, 9230–9233

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[21] CCDC 1477468 (**8**) and 1477469 (**6h**-*di*) contain the supplementary crystallographic data for this paper. These data are provided free of charge by The Cambridge Crystallographic Data Centre.

Received: May 2, 2016
Published online: June 8, 2016

